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May 18, 1998

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3127
Research Triangle Park, NC 27709

Dear Dr. Jameson:

We are hereby submitting comments on the proposed listing of tamoxifen in the *Report on Carcinogens, Ninth Edition*, in response to the Public Health Service notice published in the *Federal Register* on March 19, 1998 (63 *Fed.Reg.* 13418-20).

These comments supplement comments we have previously submitted on this matter. Those previous comments, copies of which are attached, include --

-- our February 10, 1998, letter to Dr. Larry Hart (with copies to the NTP Executive Committee, its Board of Scientific Counselors, and the Board's RC Subcommittee), commenting on the *RC Draft Background Document* and presentations and discussions at the October 30-31, 1997, public meeting of the RC Subcommittee of the NTP Board of Scientific Counselors; and

-- our April 9, 1998, letter to Dr. Kenneth Olden (with copies to four FDA officials), in which we explained important concerns with the NTP program, extending to a large extent beyond tamoxifen to pharmaceuticals generally, raised in an April 1, 1998, meeting with FDA.

Also enclosed is an update on recent scientific data pertaining to the proposed listing decision and points raised in our February 10 comments letter. Most of these data and analyses have been published since the IARC determination and have not been considered by the NTP RC review committees. We believe these additional data further support our view that there is currently too much uncertainty in the human evidence to justify describing tamoxifen as "known to be a human carcinogen".

Summary of Zeneca's Principal Concerns

1. We believe the scientific record (including the data and analyses described in the attached documents) demonstrates substantial uncertainties as to whether tamoxifen is known to cause endometrial cancer, and therefore it would be

improper and misleading to list it in the upcoming *Report on Carcinogens, Ninth Edition*, as a "known human carcinogen". We have also noted that additional pertinent data is expected to be published in the near future, and have therefore urged that a decision on listing of tamoxifen be deferred until the Tenth Edition so that all new data can be carefully examined and weighed through the full NTP review process.

2. The proposed form of the listing does not provide benefit-risk information needed by individual patients and doctors, and the simplicity of such a listing would almost surely mislead or confuse many women and interfere with attempts by FDA and NCI to communicate such information.

Announcement of the early termination of the Breast Cancer Prevention Trial and the publicity and public reaction surrounding the preliminary results from the Trial have amplified our previously expressed concerns, particularly regarding the likely public health implications of the current NTP listing proposal. Many more women will now consider taking tamoxifen, and they should be provided with full, accurate, and useful information on any benefit-risk tradeoffs in order to make a decision. It is clear that the factors involved in such a decision will vary by individual -- involving matters such as age[1] and an assessment of a range of risk factors -- and that the NTP listing not only would not provide sufficient information, but would, as indicated by the data in our April 9 letter to Dr. Olden, interfere substantially with FDA and NCI attempts to communicate such information.

It should also be noted with regard to the preliminary reports on results from the Breast Cancer Prevention Trial that the NTP listing proposal for tamoxifen, which has undergone three levels of review so far, refers only to the benefits of tamoxifen for adjuvant treatment of breast cancer, and no consideration has been given to advising the public of prevention benefits. Thus, on this aspect of the proposed listing alone, the current proposal and the review to date do not reflect up-to-date scientific information.

The Need for a Separate Category for Pharmaceuticals in the *Reports*

We believe that the current NTP treatment of FDA-approved pharmaceuticals such as tamoxifen is not adequate, and is almost sure to be detrimental to the public health, contrary to the Congressional purpose in creating the *Report on Carcinogens* Program. Therefore, we support creation of a separate category for pharmaceuticals within the *Reports*, including listing, that would provide information that is more complete and more useful and would not be likely to confuse patients and doctors.

The current NTP listing format was not explicitly dictated by Congress in the 1978 legislation establishing the Program. The legislation directed the Secretary to list substances known or reasonably anticipated to be carcinogens; it did not specify how such listing should be done. Also, the legislative directive requires that each *Report on Carcinogens* address the extent to which current regulatory standards decrease the risk

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[1] For example, the preliminary NCI reports on the termination of the NSABP prevention trial indicate that there was no indication of increased risk of endometrial cancer for women under age 50.

to the public from exposure to a listed substance.[2] In the case of tamoxifen, complying with the full legislative directive would require that NTP attempt to identify those classes of individuals for whom the use of tamoxifen would pose likely risks exceeding likely benefits, as opposed to those for whom the likely benefits would exceed the risks.[3] This level of communication is certainly not possible under the current NTP RC listing and reporting scheme, and therefore that scheme should be revised for pharmaceuticals.

We respectively urge the Secretary and NTP to open a public dialogue on creation of a new listing category for pharmaceuticals and how best to provide information on pharmaceuticals in future editions of the *Report on Carcinogens*. There are many possible options, and we believe that the NTP would benefit from input from the many stakeholders likely to have a keen interest in this issue.[4] We suggest that deliberations on this matter would best be accomplished through *a Federal Register* notice and comment process, with involvement of the Board of Scientific Counselors and its Executive Committee, and close liaison with FDA and NCI. It might be advisable to set up a specialized working group to address the matter, and to issue a preliminary public notice, or schedule a public meeting, for the purpose of soliciting views on how the deliberative process for developing this new category should be carried out.

Summary of Recommendations

1. The NTP and the Secretary should create a separate *Report* category, including listing, for pharmaceuticals that would provide more complete and useful information on benefits and risks. Public input should be solicited through formal notice and comment on the formation of this separate category.

2. The NTP should correct and expand the scientific record and conduct further review of the endometrial cancer issue, including careful analysis of the full data from the Breast Cancer Prevention Trial and the NCI-sponsored USC/Norris study that are expected to be available in the near future, along with the additional scientific material supplied by Zeneca in these and previous and future comments.

3. Tamoxifen should not be listed in the Ninth Edition of the *Report on Carcinogens*. Any listing proposal and NTP review should be deferred until the Tenth Edition,

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[2] We note again that the language of the statute and its legislative history, with references to "regulatory standards" and reducing public exposures to harmful substances, does not appear to fit pharmaceuticals. It appears the legislation was directed at other types of environmental exposures, such as those in air, water, and food, and consideration was not given to pharmaceuticals. Thus, either pharmaceuticals should be removed from the *Reports* or a way should be found to treat them differently from other substances in order to comply with the spirit of the statutory mandate.

[3] To date, the NTP listing proposal contains only information on a reduction in the risk of breast cancer through adjuvant treatment with tamoxifen.

[4] In addition to not having had an opportunity to comment on listing language concerning the benefits of prevention, the public has not had an opportunity to comment on that mandated portion of the *Report* that must provide information on the extent to which (or whether) existing regulatory controls decrease cancer risk, nor on any NTP proposal for how such information might be incorporated into the proposed listing.

because at this point there is clearly insufficient time left in the Ninth Edition cycle to carefully consider and reach decisions on how to treat pharmaceuticals in the *Reports*, and to analyze and comment on the new scientific data on endometrial cancer and submit such data and analysis to the full NTP review process. In the meantime, FDA and NCI can be counted on to provide the necessary information to patients and doctors.

We look forward to working with the NTP and its participating agencies on these important issues. We will also continue to inform the NTP of any additional significant scientific information that becomes available in the future, and will provide supplemental comments on such data.

Sincerely,

Gerard T. Kennealey, M.D.
Vice President, Medical Affairs

Enclosures

cc w. encl.: Dr. Michael A. Friedman, FDA
Dr. Richard Klausner, NCI
Dr. Bernard A. Schwetz, FDA
NTP Executive Committee
NTP Board of Scientific Counselors

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Gerard T. Kennealey, MD
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February 10, 1998

Larry Hart, Ph.D.
Executive Secretary
Environmental Toxicology Program
National Institute of Environmental
Health Sciences
MD A3-02, P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Hart:

I am writing on behalf of Zeneca Pharmaceuticals to express our company's concerns with the National Toxicology Program's (NTP) review process for the proposed listing of tamoxifen in the *9th Report on Carcinogens*. Aside from many factual inaccuracies in the NTP's documentation serving as the agency's rationale for listing tamoxifen as a carcinogen, which this letter is intended to correct, Zeneca is very concerned about several procedural problems in the NTP's review process for substances proposed for the *9th Report on Carcinogens*. Additionally, the agency has failed to consider the public health impacts of what Zeneca and many independent scientists and patient advocates believe would be a premature and erroneous listing of tamoxifen as a substance "known" to be a human carcinogen.

Tamoxifen, which we at Zeneca produce, is widely acknowledged to be a potent weapon against breast cancer. It has a long, proven history of reducing both recurrence and mortality in breast cancer patients (*16,22,23,25*). It is credited with saving many thousands of lives yearly. Tamoxifen plays a crucial role in controlling a cancer that is expected to affect nearly one million additional women each year by the year 2000 (*15*), and the World Health Organization considers it an essential therapy for this disease (*34*). Labeling of tamoxifen as a "known human carcinogen" for endometrial cancer has, as we have seen in California and elsewhere, a clear potential to deter use of this valuable drug and add to the anxiety concerning the difficult decisions that breast cancer patients and their doctors must make, with grave public health consequences (*25,31*). Therefore, we continue to urge the NTP, and its *Report on Carcinogens* review committees, to consider with the greatest care (a) whether listing of tamoxifen as a known human carcinogen is warranted by the scientific evidence and the accepted scientific norms for evaluating human evidence for causality, and (b) the broad

role given the Secretary of HHS by Congress of advising the public and Congress on whether substances cause cancer (*2*). We urge this particularly in light of the NTP's overall mandate to act as "an extension of the Public Health Service's responsibility for safeguarding the public's health." (*28*)

The fact is, numerous scientific experts and authorities, both within and outside governmental agencies, recognize that there are substantial uncertainties in the existing data regarding tamoxifen and endometrial cancer (*6,10,12,16,20,24,27,32*). Many of those observations have been published or communicated to HHS since the February 1996 IARC evaluation. It could prove gravely misleading to the public to list tamoxifen as a substance "known" to "cause" cancer in the face of those uncertainties and in the face of notice that significant new published data concerning those uncertainties are likely to be available by 1999, when such a listing would be published, or sooner.

Professor Leslie Bernstein at the University of Southern California sent comments to the NTP Board of Scientific Counselors' RC Subcommittee in which she advised the Subcommittee not only of problems with existing human studies, but also that she and her colleagues had recently completed an NCI-sponsored case-control study, expected to be published soon, which is specifically designed to examine some of those problems (*6*). The study is designed to assess possible confounding of risk estimates by estrogen replacement therapy, oral contraceptives, and obesity. She advised that the submitted study results show that risk estimates "were dramatically modified by whether or not the woman was obese and whether or not she had previously used estrogen replacement therapy," and she suggested that the published results would show that risk of endometrial cancer was not significantly elevated when such factors were taken into account (*Id.*). Written comments by Dr. Leslie Ford of the National Cancer Institute also urged the Subcommittee to consider carefully these findings from the Bernstein study (*16*). The public discussions by the RC Subcommittee on October 30, 1997, indicated, however, that at least some Subcommittee members did not appreciate the significance of the Bernstein study.

The Bernstein study does not address all of the potential problems with previous studies. Another significant issue is likely detection (or "ascertainment") bias in those studies. Tamoxifen can cause side effects that prompt gynecological examinations that will disclose tumors at a higher rate that in unexposed control groups, thereby inflating relative risk findings. Observation of these differential effects was acknowledged by authors of the 1994 NSABP study report by Fisher et al. relied on in the *Draft Background Document*, and is evidenced by data reported from the Stockholm trial (*17*). Written comments were submitted by Dr. Lawrence Wickerham, Associate Chairman of the National Surgical Adjuvant Breast and Bowel Project ("NSABP"), advising the Subcommittee of how the ongoing Breast Cancer Prevention Trial, Protocol P-1 ("BCPT") has been designed to address this issue, and that the results of the first five-year follow-up will be available in 1999 (*33*). The NSABP recommended that HHS delay its listing decision until the results of the BCPT

study are available. Dr. Ford of the National Cancer Institute also urged the NTP to consider the results of the BCPT, as well as the Bernstein study (*16*).

In view of the above, we believe it prudent for the NTP to defer listing until such data are finalized. We further believe that it is imperative that the NTP and its reviewers appraise the data on tamoxifen and formulate their listing or no listing recommendations with the following fundamental points in mind:

Basic Points Regarding the Report on Carcinogens Review Process

1. The Federal legislation mandating the *Report on Carcinogens* listing program does not, like some other Federal statutes, require the Secretary of Health and Human Services and the NTP to review specified substances within a specified timeframe (*1*). The selection of individual substances for review is left to the Secretary. It is only after it has been finally determined by the Secretary that a substance is known or reasonably anticipated to be carcinogenic that Congress mandates that the Secretary publish a list of substances for which such determinations have been made and include that substance. Thus, it is perfectly legal and appropriate for the NTP and the Secretary to defer action on an individual substance when she has good reason to believe that new data is likely to become available in the near future which will confirm or resolve uncertainties regarding the appropriate listing determination. This is especially true in the case of a substance for which a listing determination will have a significant, predictable adverse effect on public health, thus creating a result antithetical to the broad purpose of the listing program.

2. The NTP appears to have adopted a policy that it will consider and cite only published, peer-reviewed data and articles when making decisions on listing and ranking of substances in the carcinogen review program. We are unsure as to the official source or origin for such a policy at the NTP. Nor are we aware of any legally-binding directive that would prevent the NTP and the Secretary from acknowledging pertinent research in progress, or from considering its impact on the analysis at hand, particularly when that information could help resolve uncertainties or allow the NTP to avoid scientifically inaccurate listings. The NTP solicitation of public comments on the proposed listing of tamoxifen and other substances appears to recognize that unpublished information can be submitted and considered by the NTP (*14*). For that matter, we know of no directive that would prevent the NTP and the Secretary from deciding to defer a listing determination until the findings of those studies are reported in the peer-reviewed literature where they can then be reviewed as published data.

3. The legislative history for the statute clearly reflects a Congressional intent to have the Agency distinguish carefully between substances for which the evidence of

carcinogenicity is only suggestive and those for which carcinogenicity *in humans* has been "confirmed", "clearly demonstrated", and for which the data is "convincing" (*2*). In other words, in order to be listed in the "known" category, Congress clearly intended that the supporting evidence be substantially beyond "suggestive" of a causal relationship. It is also clear from the current NTP listing criteria that a listing in the "known" category requires stronger evidence than "suggestive" evidence or that "which indicates that causal interpretation is credible," as required for a category 2 listing. As a matter of fact, the original bill designated category 2 substances as "suspected carcinogens", and this terminology was changed, and enacted as "reasonably anticipated" (*3*). This was clearly an upgrading of the evidentiary standard for category 2 beyond "suspected" and, by implication, a clear statement that category 1 listings also must be supported by substantially stronger evidence than "suspected" carcinogenicity, which would be insufficient even for listing as a category 2 substance. Despite this careful choice of language, it appears that the review committees evaluating tamoxifen are interpreting the word "indicates" (in the Agency's listing criteria for category 1) as equivalent to "suggests" rather than equivalent to "confirms", "demonstrates", or "convincingly establishes" that the substance causes cancer in humans, as would be correct (*4*).

4. The "known" listing category hinges on examining evidence from human studies to determine whether it convincingly establishes a causal relationship. This means evaluating mainly evidence from epidemiologic studies. Epidemiologists distinguish carefully between mere "association" and "causal association" (or "causal relationship"), and they employ widely-accepted principles or criteria (often referred to as the U.S. Surgeon General's or Bradford Hill criteria) for making judgments on whether the human evidence is sufficient to support a determination of causal association. This distinction, and the principles or criteria for making judgments regarding causation, appear to be very blurred or unrecognized and unutilized in the NTP review of tamoxifen to date. This is almost surely due to the scarcity of epidemiologists on the NTP review committees (*35*).

   Among the important principles or criteria for making causal judgments, as set out by the U.S. Surgeon General (*13*) and many others (*e.g., 11,26,30*), are --

   a. The consistency of the association through repeated observations in multiple and differing investigations

   b. The strength of the association across studies in terms of the relative risk ratio (an RR of less than 2.0 or 3.0 being generally considered "weak")

   c. The specificity of the association with a defined disease state or states

d. The temporality of the association (whether the disease clearly follows the exposure -- *i.e.*, effect following cause -- within a biologically reasonable period), and

e. The coherence of the association with human biological and surveillance data

Other criteria often invoked and examined include whether the data evidence a "biological gradient" (or "dose-response" -- sometimes considered an aspect of "coherence" and "strength"), and whether the relationship is "biologically plausible" (a variation on the "coherence" criterion).

Application of these criteria is important to ensure the scientific accuracy of the NTP listings. However, from the NTP written and oral presentations, as well as from the composition of the review committees and statements made by individual committee members, it seems that the analysis to date has not rigorously applied these commonly-accepted criteria. As other examiners have noted, and as discussed further below, the human evidence as a whole falls far short of establishing a causal relationship for numerous reasons. These reasons include --

-- a clear lack of consistency across the body of epidemiologic studies, with the effect of a large body of negative, null, or statistically insignificant findings given little or no weight

-- even among the studies with positive findings, lack of strength in the relative risk findings; and even when they appear strong, as in the Fisher et al. study, the findings have, upon further review, been found to be weak (*12*)

-- substantial uncertainty regarding temporality due to likelihood of detection bias resulting from unmasking of pre-existing or synchronous tumors due to more careful examination of study subjects receiving tamoxifen than the control groups

-- lack of coherence in human biological data due to tamoxifen also being recognized as effective in treating endometrial cancer, and in surveillance data due to the apparent lack of elevation in incidence in study findings above normal population incidence

5. The principles or criteria for causality discussed above are most commonly used to evaluate the evidence from a body of studies, although they have more limited application in evaluating individual studies. In addition to examining the total body of

studies with those principles or criteria, those evaluating the evidence must also, however, consider the quality of the individual studies, and particularly whether their results could have been due to bias, confounding, or chance (*11,13,26,30.*). The probative value of various individual positive tamoxifen studies is limited by a failure or inability to rule out one or more clinically relevant potential sources of confounding or bias. Further, as discussed below, the manner of data collection and analysis artificially inflated some of the risk estimates reported from the studies. Although these limitations were often acknowledged by the study authors themselves, the NTP committee comments and recommendations were conclusory and dismissive regarding such concerns.

The NTP listing criteria specifically require that substances be listed no higher than the "reasonably anticipated" category if "causal interpretation is credible, but that alternative explanations such as chance, bias, or confounding, could not adequately be excluded...." The criteria thus place an affirmative burden on the NTP and the Secretary to ensure that alternative explanations have been adequately explored and ruled out. The record of NTP review does not reflect this thoroughness, and a more cautious and highly critical analysis of these factors should be of particular priority to the NTP and its committees.

6. Listing as a "known" human carcinogen requires that the listing be based on evidence "from studies in humans which indicates a causal relationship...." While the RC listing summary at the beginning of the *Draft Background Document* contains a statement to this effect, the summary then asserts that its conclusion regarding tamoxifen is supported by evidence from experimental animal studies and mechanistic data, including *in vitro* data. It appears that NTP officials and reviewers may be under the impression that it is permissible to consider such non-human evidence in support of a category 1 ("known") listing. The likelihood of this appears high particularly in view of the weakness of the evidence from human studies, as discussed above. If the reviewers have been operating under such an assumption, we believe it can be shown conclusively that such a view is erroneous and would invalidate the listing decision. Only "evidence from human studies" should be discussed in connection with possible listing in the "known" category; if evidence from non-human studies is to be considered, it must be in connection with the "reasonably anticipated" category or a recommendation or decision not to list. The *Draft Background Document* should reflect this distinction.

7. At the October 30-31 listing review meeting, RC Subcommittee members indicated that they thought the Subcommittee was confined to a very limited role: voting "Yes" or "No" on the views and recommended listings set forth by the RG1 and RG2 committees and contained in the *Draft Background Document.* The basis for this belief is unclear; we are not aware of any written "charge" to the Subcommittee or

other reviewers which so restricts their scientific judgment and recommendations. The NTP's documents describing the listing review process are broadly worded rather than restrictive. Additionally, if the issue raised for the review groups is simply whether to list, as was the case with tamoxifen in the July 11, 1997, *Federal Register* notice (*14*), then the RC Subcommittee and the other reviewers should be able to go beyond voting simply "Yes" or "No" on a category 1 listing and recommend deferral of a listing decision, no listing, or listing in category 2.

8. The *Report on Carcinogens* review process is not delimited by the legislation. It appears that Departmental policy states that certain committees will be included in the review process, but the process anticipated by the legislation does not exclude the possibility of additional review entities. Therefore, we believe there exists a great deal of discretion to modify or supplement the process at any time, for any specific substance, where the Secretary or her delegatees determine that this would further the broad goals of the program. In this instance, it appears necessary and appropriate to convene an additional blue-ribbon panel whose membership includes a substantial number of experts with strong credentials in reproductive epidemiology and gynecology relevant to the issues under consideration.

More Specific Points Regarding the NTP Review of Tamoxifen to Date

It is also fundamental that the scientific data or commentary on tamoxifen (or any other substance undergoing NTP review) must be presented fully, fairly, and accurately. The *Draft Background Document for Tamoxifen* contains a number of inaccuracies, omissions, and deficiencies that should be corrected:

1. The *Draft Background Document* listing summary (RC-1 to RC-2) states that Professor MacMahon concluded that the studies were "suggestive of a causal association ... but were not conclusive because of confounding . . . ." (Emphasis added) This statement is inaccurate. Professor MacMahon did not conclude that the evidence suggests a causal association; he concluded that the studies "suggest that an association . . . exists." (*27, emphasis added*). The distinction between causal association and simple association is important and widely recognized, as noted above. It is noteworthy that Professor MacMahon (an eminent breast cancer researcher), sub-titled his article "Perspectives of an Epidemiologist". After the above statement, he went on to state that even the evidence of an "association" was "far from conclusive" and "incomplete", and that "legitimate questions can still be raised about the relationship . . . and particularly about whether the relationship, if real, is a causal one." (*At 136, emphasis added*). Professor MacMahon should be quoted fully and accurately in the *Draft Background Document*, and attention should be drawn to the essential distinction between "association" or "suggested association" and a known "causal relationship".

2. The *Draft Background Document* omits discussion or reference to other peer-reviewed articles which, like Dr. MacMahon's, have been published since the 1996 IARC review and point out the serious problems with existing human studies, the insufficiency of the evidence to support a causal inference, and the lack of relevance of the animal and *in vitro* data (*8,10,12,15,20*).

3. One of the most prominent issues raised by Professor MacMahon (among others) is that it is likely that use of unopposed hormone replacement therapy ("HRT") by study subjects has confounded many of the human studies on tamoxifen. The NTP, in its summary of the *Draft Background Document* (section entitled "Other Information..."), does recognize that it has been demonstrated that such HRT exposures pose "a highly elevated risk for endometrial cancer". However, we note that the significance of this observation is far more central to the analysis of the tamoxifen human evidence than placement in the "other information" section would suggest. This acknowledgment of potential for substantial confounding belongs in the first section of the summary where the human studies are discussed, with an explanation that substantial confounding by unopposed HRT, as suggested by Professors MacMahon, Bernstein, and others, remains a distinct possibility despite IARC's unexplained dismissal of the issue.

4. The *Draft Background Document* summary omits any mention of the fact that tamoxifen has been identified by the World Health Organization since 1994 as the only pharmaceutical essential to the treatment of endometrial cancer (*34*). This WHO recognition was based upon an extensive body of human evidence. The 1996 IARC monograph review of tamoxifen very briefly noted only a few such studies, did not reference the WHO finding, and did not discuss the significance of this information. More recent reviews continue to confirm WHO's 1994 finding (*10,12,19*). And this evidence from human studies is directly pertinent to the major causality criteria of "consistency" and "coherence" among human studies. As Dr. Carmel Cohen of Mt. Sinai School of Medicine recently observed after reviewing such data, "it is difficult to reconcile this tamoxifen effect with the notion that it is a drug that initiates and promotes the replication of endometrial cancer, for clearly it has a therapeutic role in this disease." (*10*) This point also suggests that the *Draft Background Document* is mistaken in stating that tamoxifen is likely to have the same effect as conjugated estrogens in the human uterus.

5. The *Draft Background Document* should acknowledge that the effect of detection (or "ascertainment") bias has not been explored in existing published studies, that clinical trials data suggest this effect, and that studies are now under way to evaluate it (*e.g.*, the BCPT, discussed above). The issue of detection bias is highly significant, and it coincides with the causation criterion of "temporality", which is the one criterion that

is absolutely essential to a finding of cause-effect relationship. That is, if the cancer existed undetected prior to the use of tamoxifen, the effect cannot have followed the putative cause, and the causal criterion of "temporality" is not satisfied. The likelihood of such bias is further supported by point 6, below.

6. The *Draft Background Document* should inform the reviewers that the incidence of endometrial cancer observed in breast cancer patients treated with tamoxifen is virtually the same as seen with routine screening for endometrial cancer, as noted by Dr. Jordan of the Robert H. Lurie Cancer Center in his written comments to the RC Subcommittee (*24*). The *Draft Background Document* should also explain the significance of this point with regard to the issue of potential detection bias and the effect it would have on apparent positive study findings to date.

7. The *Draft Background Document* places particular emphasis on three studies that are all either substantially flawed or given unwarranted weight:

   -- The Curtis et al. 1996 cohort study is described as having found a statistically significant elevation in the risk of endometrial cancer "in women who had received tamoxifen therapy". As Professor Bernstein explained in her written comments to the Subcommittee, based on her intimate experience with NCI SEER data it is clear that the Curtis study used SEER registry information that was unclear as to whether women were exposed or unexposed specifically to tamoxifen. Such women may not have received the antiestrogen tamoxifen, may have been exposed to another hormonal therapy, or may not have received any medication that interrupted or altered the patient's hormonal status (*6*).

   -- The two key clinical trials (among fourteen) that showed a statistically significant elevation in risk (Fisher et al. 1994 and Rutqvist et al. 1995) are described by the NTP as "strong". However, as Dr. MacMahon noted in his review, the number of endometrial cancers in the control groups for both studies were unexpectedly low, which would have had the effect of artificially inflating the findings (*27*). Additionally, some clinical studies used control groups drawn from the general female population, when such a comparison is not appropriate because breast cancer itself has been shown to be associated with an increase in endometrial cancer (RR of 1.72,*5*). Like others, Dr. Creasman has examined the data from the Fisher et al. study and concluded there are sound reasons for concluding that the findings were either not positive or only weakly positive (RR of 1.0 to 1.7 rather than 7.5 (*12*). Such studies cannot be described as containing "strong" findings when there are identifiable problems with the representativeness of the control groups and classification of cases, and the *Draft Background Document* should contain this point.

8. The *Draft Background Document* acknowledges the lack of positive findings in the other twelve clinical studies, but it dismisses those findings with the observation that their combined results shows 29 cases of endometrial cancer in patients receiving tamoxifen versus 14 in controls. Such arithmetical "combining" to obtain a summary number without regard for careful qualitative analysis of the individual studies, discussion of variations in individual study outcomes, or exploration of uncertainties and assumptions, is a controversial approach and is likely to amplify biases and/or confounding that were present in individual studies (*7*). There should be a fuller explanation and justification of such an approach in the *Draft Background Document*, or else the "combining" approach results should be removed.

9. The summary portion of the *Draft Background Document* states that in the study by Cook et al. (1995) "no increase [in risk] was seen . . . ." To be accurate, it should state that the study actually found a <u>decrease</u> in the incidence of endometrial cancer in tamoxifen-treated women.

10. With regard to animal data, the *Draft Background Document* states that they "also provide evidence of tamoxifen's carcinogenic effects." This statement is very misleading, suggesting that tamoxifen has been shown to induce endometrial cancer in animals. All of the appropriately conducted animal experiments have shown that tamoxifen is associated with no increase in endometrial cancer in laboratory animals. Only two studies could be considered even remotely supportive of the statement in the *Draft Background Document*. One of those was conducted on neonatal mice, which do not provide a sound model for inferring similar effects in humans. The second such experiment (on rats) used a non-standard protocol and has not been reproduced and validated. These important qualifications should be explicit in the *Draft Background Document*, and it should be acknowledged that the animal data demonstrate a complete lack of predictiveness of adverse health effects in humans (*20*).

11. The statement in the "Other Information . . ." portion of the summary portion of the *Draft Background Document* that "tamoxifen would likely produce the same effects as conjugated estrogens in the uterus" (*i.e.*, increases in endometrial cancer) is simply wrong. Recent data show that tamoxifen produces effects on the human uterus different from those of estrogen (*10,12*). These data are consistent with the data showing the value of tamoxifen for <u>treating</u> endometrial cancer. It should be noted that much of the data were not available at the time of the February 1996 IARC review.

12. The *Draft Background Document* should openly acknowledge, as do the authors of the study, that the findings of Hemminki et al. with regard to DNA adducts in human tissue have not been found by other investigators (*10,11*), and that Hemminki et al.

acknowledged in their work that they could not be certain from their data that the adducts they observed were actually attributable to endometrial tissue (*21*).

Actions Requested

1. We request that changes in accordance with the above observations be made to the review presentations and record.

2. We request that NTP terminate its current review of tamoxifen and defer further review until consideration of the *Tenth Report on Carcinogens*. With so much at stake in terms of the potential public health consequences of its listing action, the NTP should exercise great caution in view of the serious issues regarding uncertainties that have been raised and the likely availability of significant data to confirm or resolve those uncertainties by the time reviews for the *Tenth Report* commence in 1999.

Sincerely,

Gerard T. Kennealey, M.D.
Vice President, Medical Affairs

cc: Dr. C. W. Jameson
Members of the NTP Executive Committee
Members of NTP Board of Scientific Counselors and
its RC Subcommittee

REFERENCES AND NOTES

1. For example, sec. 112 of the Clean Air Act, 42 USC 7412, contains a list of substances and sets out specific timeframes within which EPA must act to regulate those substances.

2. H.R.Rep. No. 95, 95th Cong., 2d Sess. at 28 (May 15, 1978); Cong. Rec. H-34938 (Oct. 10, 1978). The legislative provisions came from the House bill and the House-Senate conference; there were no relevant provisions in the Senate bill.

3. The House bill mandated publication of a list of "known or suspected carcinogens", while the final Act changed this to "are known to be carcinogens or may reasonably be anticipated to be carcinogens. . . ." Compare sec. 306(c)(10) of H.R. 12347 as reported in H.R. Rep. No. 95, *supra* n. 2, with 42 USC 241(b)(4), and see the Joint House-Senate Summary and Explanation, 124 Cong.Rec. H13566, Oct. 14, 1978.

4. In this connection, it should also be noted that the plain language of the legislation appears to indicate that Congress did not intend that the Secretary and the NTP would review pharmaceuticals. The statute directs the Agency to review the "effluent, ambient, or exposure standard" established by a Federal agency for each substance reviewed, and the extent to which such standard "decreases the risk to public health from exposure to the substance. . . ." This language appears to be aimed at involuntary exposures from substances in media such as air, water, soil, and food, rather than pharmaceuticals administered under medical supervision, and could be so interpreted by the agency. If Congress had intended to cover pharmaceuticals, it would have likely used the term "dose".

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8. Carmichael et al., "Lack of genotoxicity of tamoxifen in the human endometrium", *Canc. Res.* 56:1475-79 (1996).

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15. Forbes JF, "The Control of Breast Cancer: The Role of Tamoxifen", *Semin. Oncol.* 24(1)(Supp. 1):5-19 (1997).

16. Ford LG (National Cancer Institute), letter dated Oct. 23, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*, and attached letter dated October 30, 1995, to Ms. Catherine Caraway of the California Office of Env. Health Haz. Assess.

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18. Fornander et al., "Effects of tamoxifen on the female genital tract", *Annals N.Y. Acad. of Sc.* 622:469-76 (1991).

19. Gelman EP, "Tamoxifen for the treatment of malignancies other than breast and endometrial carcinoma", *Semin. Oncol.* 24(1)(Supp. 1):65-70 (1997).

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23. International Agency for Research on Cancer, "Tamoxifen", *IARC Monographs on the Eval. of Carc. Risks to Humans* 66:253-365 (1996).

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25. Langer AS (Natl. Alliance of Breast Cancer Organizations), letter dated Oct. 29, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

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30. Schlesselman JJ, "`Proof' of Cause and Effect in Epidemiologic Studies: Criteria for Judgment", and references therein, *Prev. Med.* 16:195-210 (1987).

31. Steinberg M (Zeneca Pharmaceuticals), letter dated Oct. 24, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

32. "Tamoxifen & The Uterus: Potential Uterine Risks of Anti-Oestrogens" International Meeting Organized by: The Flemish Work Group Gynecological Oncology and the Dept. of Obstetrics & Gynecology of Algemenene Kliniek, St-Jan Brussels, December

12-13, 1997. The consensus during this meeting was that the data, including new data presented at the meeting, are sufficient only to indicate an association, not a causal relationship. The abstracts from the meeting will be published in the near future in a supplement of *The European Journal of Cancer*.

33. Wickerham DL (Natl Surgical Adjuvant Breast and Bowel Program), letter dated Oct. 23, 1997, to Dr. Larry Hart and the NTP Board of Scientific Counselors RC Subcommittee containing comments on the July 11, 1997, NTP proposal to list tamoxifen in the *9th Report on Carcinogens*.

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35. The legislative history of the law requiring the *Report on Carcinogens* does not reflect a Congressional intent to give leadership of the program to the National Institute of Environmental Health Sciences or the National Toxicology Program (administered by NIEHS). While the final Joint House-Senate Summary and Explanation (see note 3, above) indicates that the NTP was expected to play a major role, the Congressional delegation is to the Secretary, and the Summary and Explanation indicates appears to give at least as much emphasis, if not more, to the roles of the National Cancer Institute and the Food and Drug Administration. This makes sense because listings in the "known" category require epidemiologic expertise, and the scientific expertise of the NTP is primarily in the conduct and interpretation of animal experiments, while NCI and FDA have more experience with human studies.

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William J. Kennedy, Ph.D.
Vice President
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April 9, 1998

Kenneth Olden, Ph.D.
Director
National Institute of Environmental
Health Sciences
National Institutes of Health
P.O. Box 12233
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Dear Dr. Olden:

The National Toxicology Program, since its inception, has contributed significantly to the identification of numerous carcinogens which had unnecessarily exposed thousands of Americans to risk. The review, evaluation and listing process has not only reduced the exposure of the public to environmental hazards, but also identified hazards in the work place. Through this effort, the program has been successful in contributing to greater protection of public health in this country, and through its position as a leader in this area, probably the world. Another major contributor to the reduction in cancer rates, and the mortality associated with this disease, has been the result of other programs such as the early detection programs, cancer awareness programs by many public and private organizations, as well as some significant advances that have been made by the government, academia and the pharmaceutical industry in providing detection and treatment options that were not available 20 years ago. It is this latter aspect that I would like to focus upon in this partnership that all of us have in reducing the risk and attendant mortality associated with cancer.

On April 1, 1998, representatives from Zeneca Pharmaceuticals, Wilmington, DE, had the opportunity to meet with senior staff of the FDA to engage in dialogue on this issue. Specific to our discussion was the proposed NTP listing of tamoxifen as an agent known to cause cancer. However, during our discussion, it became clear that there is a more significant problem which extends beyond tamoxifen. The issue became apparent as we attempted to reconcile the NTP listing of tamoxifen or other drugs of this nature with a specific section of the mandate published in the March 19, 1998, Federal Register Notice which states:

> "The law also states that the report (*Report on Carcinogens, Ninth Edition*) should provide available information on the nature of the exposures, the estimated number of persons exposed and the extent to which implementation of the Federal regulations **decreases the risk** to public health from exposure to these chemicals." (emphasis added)

It is our belief that NTP listing of tamoxifen at this time will actually increase the risk to the public health rather than decrease it. The basis for our concern is an assessment of previous experience that Zeneca had during 1996.

NOLVADEX®, Zeneca's brand of tamoxifen, has been available in the United States since 1978. During the time it has been available, its acceptance by physicians and patients has grown steadily. This growth has also been due in part to continued research and development by ourselves as well as NCI, academic and cooperative groups in supplemental indications for use. In 1996, there was a precipitous change in the usage pattern of tamoxifen. Instead of continuing on its previous growth curve, usage actually decreased for the first time since it was introduced in the U.S. We roughly estimate from total tablet sales that the decrease in usage could be equivalent to about 30,000 patients stopping their medication between 1995 and 1996. The estimate of the number of patients affected was even more dramatic if the projected usage in 1996 is considered, probably approaching 40,000 patients.

Zeneca carefully evaluated this unprecedented decline. A thorough review of the regulatory approval activity of the FDA confirmed that no new breast cancer treatment was approved in that time frame. There were, however, three events which took place in the latter half of 1995 and first part of 1996, when examined in detail, caused us some concern which we subsequently examined more closely. These three events were the publication of the NCI-sponsored long-term tamoxifen treatment trial B-14, the listing of tamoxifen under Proposition 65 in California as a carcinogen, and the almost simultaneous listing of tamoxifen by IARC as a carcinogen. Adding to the actual listings, there was a concurrent rash of "sensational" journalism in the popular press, with such sensationalistic headlines as ***"Cancer drug causes cancer"***.

Our market research results, gathered from interviews with both patients and physicians, confirmed that during this period of time, the time of the Proposition 65 activity and the IARC listing, there were a meaningful number of patients who stopped taking tamoxifen because of the fear generated by these headlines. To its credit, IARC when issuing their press statements, made very clear references to the benefits of tamoxifen in the treatment of breast cancer. Unfortunately, none of the headlines and few of the news articles or reports included this balanced statement. Of particular concern not only to Zeneca but also to physicians, was our market research finding that many women stopped taking the drug without consulting their physician.

Tamoxifen was and still is the only drug approved for adjuvant use. These patients are all women who have been previously diagnosed with breast cancer, have had primary treatment either with surgery and/or chemotherapy or radiation, and are given tamoxifen in an adjuvant setting. For the most part, they believe they have been cured of the disease in the primary treatment, feel they are taking tamoxifen "just in case the physician didn't get it all", and most importantly are asymptomatic. They had entered onto tamoxifen therapy only after having discussed it with their physician, needing a prescription, but they needed no such consultation to stop taking their oral medication.

This is a central problem in the public health risk of an NTP listing of tamoxifen at this time that Zeneca and FDA identified on April 1, 1998. The experience in 1996 would indicate that some portion, probably a large portion, of the women stopped taking tamoxifen because of fear, and this put some of them at risk.

The concerns shared by FDA and Zeneca led us to mutually agree that the most prudent course of action at this time would be to recommend a postponement of the listing of tamoxifen until such time as all of the data are available regarding the risk to humans. Since our meeting with FDA, the NCI has halted the P-1 Prevention Trial, which demonstrated a favorable effect of tamoxifen in the prevention of breast cancer.

FDA raised the subject of the need to create a new, separate category for drugs proposed to be listed by the NTP as carcinogens. This additional listing category could provide definitive information on the overall risk to humans who are taking these types of medications in a prescription drug setting, without diminishing the usefulness or importance of the listings that have identified carcinogens in the environment or the workplace.

Postponement of the NTP listing of tamoxifen would allow FDA, NTP and Zeneca if you wish, to engage in discussions that could result in a recommendation for a separate listing for pharmaceuticals that are tumorgenic and present a risk as identified by the NTP, but because of their positive benefit/risk ratio, as determined by FDA, decrease the overall risk to the public health while not diminishing the warning to the general population who may encounter such compounds in the environment or the workplace.

NTP has established itself over the past 10 years as the premier authority in risk assessment of tumorgenic compounds. During this same time, the FDA has proven itself to be the premier authority in benefit/risk assessment, particularly in regard to drugs for serious or life threatening diseases, for AIDS-related diseases and in particularly for the significant advances that have been made in getting cancer treatment drugs to patients more quickly. With this history of accomplishment, it is appropriate that these two expert groups combine their strengths to prepare the next chapter in this public health effort. The opportunity to build upon their joint expertise to restructure the Report format to address this unmet need for education on this class of compounds should not be overlooked.

Zeneca Pharmaceuticals is one of the nation's leading providers of oncology products and oncology care. As a company that would anticipate having several products included on such a new list, we would endorse any effort that the government could undertake that would add clarity to what will become misleading information unless appropriate steps are taken.

We would make ourselves available to discuss this further should you determine it to be necessary.

Sincerely,

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs

cc: Bernard A. Schwetz, D.V.M., Ph.D.
Interim Chief Scientist
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SUPPLEMENTAL COMMENTS OF ZENECA PHARMACEUTICALS ON THE *RC DRAFT BACKGROUND DOCUMENT FOR TAMOXIFEN* AND THE PROPOSED LISTING OF TAMOXIFEN IN THE *REPORT ON CARCINOGENS, NINTH EDITION*

May 18, 1998

INTRODUCTION

Zeneca Pharmaceuticals, the manufacturer of tamoxifen citrate ("tamoxifen" or Nolvadex®) is providing this document as an update of the scientific data previously reviewed and provided to the Report on Carcinogens review committees regarding tamoxifen. This paper addresses original studies, significant reviews, and consensus data not previously addressed at the October 30, 1997 public meeting of the RC Subcommittee of the NTP Board of Scientific Counselors, in the *Draft RC Background Document* (dated Sept. 29, 1997), or in written comments by Zeneca on the *Draft Background Document* and in conjunction with that forum. (Copies of prior Zeneca comments are also attached as indicated in the cover letter to these comments.)

Are the conclusions of the NTP's *RC Draft Background Document for Tamoxifen*, and the recommendation that tamoxifen be listed as a known cause of human cancer, scientifically sound? So long as the true nature of the relationship between tamoxifen treatment and endometrial cancers diagnosed in treated patients remains insufficiently explained, SHOULD tamoxifen citrate be so listed? Is such a listing appropriate in light of the Report on Carcinogens Program's fundamental mission to aid in the protection public health by alerting the public and Congress to the need to reduce exposures to harmful substances? We present this supplemental data with these issues in mind. We at Zeneca continue to urge that for the Secretary of HHS, the Report on Carcinogens Program and its participating agencies to declare that tamoxifen is a substance not merely *suspected*, but *known*, to *cause* human cancer is, at best, premature. Such a conclusion presupposes a level of supportive scientific evidence that does not yet exist. We believe our position is consistent with the current state of published literature and the positions published by other reviewers of the existing data on tamoxifen and human cancer as set forth herein.

HUMAN DATA ON HUMAN CANCER:

Contemporary reviewers of the existing human studies on tamoxifen use are concluding that existing research remains inadequate to define the etiologic role tamoxifen plays in the development of any endometrial cancers diagnosed in tamoxifen-treated breast cancer patients

More than 10 million patient years of tamoxifen experience have accrued in the treatment of breast cancer. Notwithstanding this extensive clinical experience, there remains no clear demonstration that tamoxifen is a cause of human cancers. Contrary to the preliminary conclusions in the *Draft Background Document* and the RC committee reviews to date, and IARC's February 1996 classification, many scientists now concur that evidence for a causal connection has *not* been adequately established.

A far different consensus on tamoxifen and endometrial cancer has recently begun appearing more prominently in the published literature. That view, as was stated by Dr. MacMahon, is that the evidence on this issue is "far from conclusive" and that there are "legitimate questions" about whether there is a causal relationship (*1*). Similar conclusions have recently been reached by other reviewers and investigators, such as: "Further research needs to be done to uncover the role of tamoxifen in the etiology of endometrial cancer." (*3*) "A causal association has not been proven (nor even strongly indicated) for tamoxifen and endometrial cancer, and further investigation, with less bias, will be required to resolve the question."(*11*)

In December, 1997, an international meeting was held in Brussels, Belgium to discuss the effects of tamoxifen on the uterus. Almost 300 participants from 18 countries were in attendance. At this conference, "[t]here was a demand for better study design, cautious interpretation of results, and unbiased reporting."

The association between tamoxifen and endometrial cancer, concluded one review of data presented at those proceedings, "depends on host factors and is controversial."(*4*)

The concerns of the scientific community are well-defined. To begin with, only a minority of randomized trials have reported statistically significant increases in observed endometrial carcinomas. A much larger number of smaller trials have failed to observe the same association (*7*). There are also "strong selection and information biases" likely in the majority of case-control and cohort studies that have been conducted to date (*7*). These likely biases and other inherent limitations of the existing body of clinical trial and other epidemiologic data require that the issue of causation be addressed with caution, giving very careful attention to such concerns.

Since the October 30, 1997, RC Subcommittee meeting on tamoxifen, there has been only one new original human study published that we are aware of, and that study is important because it is also the only one of which we are aware that was designed specifically to address the concerns regarding potential detection bias and confounding (or "effect modification") by prior use of estrogen replacement therapy. The study, by K. Katase et al., published in the journal of the American Cancer Society on May 1, 1998 (*8*), included 825 patients with primary breast carcinoma, of whom 279 received tamoxifen as adjuvant therapy. All 825 patients had not received any prior estrogenic hormone replacement therapy, and all had endometrial examinations yearly, even if they had no gynecological symptoms. Thirteen of the 825 patients were subsequently diagnosed with endometrial cancer. The study found that there was no increase in relative risk, nor worsening prognosis, for endometrial cancer among the tamoxifen-exposed patients (RR of 1.0001). Because of the significance and newness of this study, we are enclosing a copy.

As we complete these comments, we have been informed that a new meta-analysis of the benefits of long-term tamoxifen therapy as adjuvant treatment will be published on May 15 by the Early Breast Cancer Trialists' Collabortive Group. We will not have time to examine that study and develop and include carefully-considered views on it in these comments; however, we expect to do so in the near future as we continue to provide timely updates to the NTP. We would note, however, that our preliminary information is that the analysis is based on pre-existing studies that were not designed to exclude or take into account the bias and confounding issues of concern.

Finally, we note that some preliminary results have been released from the recently-terminated NSABP Breast Cancer Prevention Trial. However, neither the published study report nor the primary data are available yet, and therefore we cannot include adequate analysis in these comments. When the published report and data are available, we would expect to provide the NTP with our analysis of these data also when feasible.

1. A lack of baseline endometrial data, insufficient latency and the verified benign gynecologic effects of treatment (leading to a diagnostic bias) remain legitimate concerns that affect the interpretation of tamoxifen data. The influence of these factors affects not only the stability of the statistical risk estimates themselves, but also any conclusions that can be reached from the data regarding the biological significance of those risk estimates. Zeneca is not alone in urging that these data collection problems raise persistent and unresolved issues in the evaluation of the endometrial cancer issue now before the Report on Carcinogens Program.

Participants in the recent large international conference on tamoxifen in Brussels, noted above, focused on the fact that "[t]here is evidence that some endometrial cancers reported in patients on tamoxifen had been present before the women started taking the drug."(*4*) At that conference, Professor Lewis Smith further noted that it would be inaccurate to say tamoxifen causes endometrial cancer. Among the reasons for this conclusion was the fact that a large percentage of the endometrial cancers reported in the key studies were diagnosed during the first two years of tamoxifen therapy (*9*). Such observations are more consistent with a mechanism in which the use of tamoxifen results in increased diagnosis of pre-existing, occult endometrial tumors than with a cause-and-effect relationship.

Current literature continues to emphasize the fact that none of the clinical trials were designed to assess whether tamoxifen caused endometrial cancer in treated patients (*7*). For the two largest clinical trials, no data at all was collected concerning the initial endometrial status of tamoxifen and non-tamoxifen patients. This deficit similarly plagues the majority of reported prospective studies. Recent researchers

have therefore concluded that the possible influences of bias cannot be ignored (*3,7,10*). RC listing category one requires (by inference from the definition of category two) that bias be adequately excluded.

As stated in one of those current publications--

> Studies evaluating the relationship between tamoxifen and endometrial pathology are fraught with problems. In most cases, these studies were not designed to assess this association and many lack a control group. Breast cancer patients inherently have an age-dependent increase in endometrial cancer risk, and their risk for benign endometrial changes has not been evaluated. Tamoxifen itself produces gynecologic symptoms that lead to increased intervention, and thus a detection bias may result. (*3*)

The specific impact of these issues upon various clinical trials are summarized in more than one recent detailed analysis (*1,12*) The current view of many cancer experts appears to be that these three problems, (a) unknown prevalence of preexisting endometrial changes (including silent or occult cancers); (b) insufficient latency for the development of some cancers attributed to tamoxifen; and (c) the verified differential effect of tamoxifen-related gynecologic symptomatology (leading to a likely detection bias), have clearly infected the issue of causation that is before the Report on Carcinogens Program.

2. Confounding and the effects of other endometrial cancer risk factors also remain valid, unresolved concerns affecting any attempt to assess the meaning of the reported tamoxifen-endometrial cancer association. It is widely acknowledged that risk factors such as hormone replacement therapy have not been taken into account in these studies (*3,4,7*). Whether there is a causal relationship between tamoxifen use and endometrial cancer therefore remains "controversial" in part because existing studies have failed to sufficiently account for the influence of other risk factors on the relative risk of endometrial cancer calculated for these groups (*4*)

"[S]ince none of these clinical trials were designed to assess endometrial cancer as an outcome, risk factors for endometrial cancer such as previous hormone-replacement therapy, were not recorded." (*7*) There is also evidence that at least some of the reported cancers "were related to other risk factors, such as obesity and past oestrogen-replacementtherapy"(*4*).

It would be inappropriate to ignore the many expressions of concern in the current literature that it is likely that the influences of confounding, detection bias, and other factors have affected the size and biological interpretation of risk estimates reported from currently published study data.

3. The relative risk estimates from existing studies that have found some association are low, and therefore very susceptible to the influences of bias, confounding, and chance. Some RC reviewers have indicated that a relative risk of 7.5 is a reliable risk estimate, and that a RR of such strength effectively rules out bias and confounding (*6*). However, recently published reviews have seriously questioned the accuracy of this finding, which came from a single study.

The estimate specifically cited by the NTP reviewers at the October 30, 1997, public meeting is one calculated from analysis of the NSABP B-14 clinical trial data. Its instability was, from inception, acknowledged by the study investigators. Those investigators subsequently recalculated the RR using SEER data because of an artifact in their original data -- an artificially, unrealistically low incidence of endometrial cancer in the original comparison group. This recalculation produced a substantially smaller relative risk of 2.2 (*5*). A number of recent reviewers and researchers have accepted this recalculated RR as the more appropriate estimate (*12,7,10*). Further review by another researcher, as pointed out in previous comments, has also revealed additional problems with the calculation of the relative risk in that study, based on mistakes in diagnosis and case v. control classification, that apparently would further weaken the estimated association significantly (*11*).

The weakness of the risk estimates calculated from other large studies has been similarly commented upon by various contemporary investigators. Study-by-study, "[m]ost risks cluster near unity or under three, especially if appropriate controls are used." (*12*) Stated in other terms, many current experts are of the view that the studies indicate a risk of being diagnosed with endometrial cancer on the order of about two cases per 1,000 patients per year (*2,3,7,13*).

The smaller size of this risk estimate is obviously of great importance to the Report on Carcinogens listing deliberations. Problems in study design and data collection are potentially of greater significance when interpreting statistical risk of this size. Weak associations such as appear to be present in this instance are consistent with an interpretation that the association is due to bias, confounding, or chance, and result from the failure of study designs to take such factors into account. Indeed, NTP reviewers have implicitly acknowledged that the effects of confounding and bias are not easily ignored when the risk estimate is in this range (*14*).

4. There is no persuasive mechanistic explanation that would support the hypothesis that tamoxifen has a carcinogenic effect on the human endometrium. Researchers have demonstrated no mechanism of action to explain how tamoxifen actually acts on the human uterus or that it causes the endometrial cancers observed in association with its use. It is still uncertain whether tamoxifen has any effect at all on the initiation of cancer or on the progression of pre-existing lesions from benign to malignant, noncancerous to cancerous, in the clinical patient. Although experimental data have raised a suggestion that tamoxifen might encourage growth of existing endometrial cancers, this theory has not been validated in the clinical situation.

One mechanistic theory suggested by the NTP in the *Draft Background Document* and in review discussions is that the endometrial cancers seen with tamoxifen treatment are caused by a partial estrogenic action of tamoxifen on the human uterus. However, whether this is true "or if tamoxifen leads to earlier clinical manifestation of pre-existing `second primaries' or precancers" remains unanswered, according to current researchers (*10*). Data impugning this theory have recently been reported from a prospective nonrandom study. Presenting their findings at the 1998 International Conference on Adjuvant Therapy for Primary Breast Cancer, researchers concluded that their results appeared, instead, "to support the theory that postmenopausal women have pre-existing lesions that may earlier become symptomatic if tamoxifen is used". (*15*)

Other data recently highlighted in the literature raise other questions regarding the credibility of purported carcinogenic mechanisms in the human uterus. Current investigators have taken note that cytogenetic changes in endometrial polyps and DNA content in endometrial cancers from tamoxifen patients are the same as those observed in patients who did not undergo tamoxifen therapy (*4*).

Still more new data seem to contradict the hypothesis that tamoxifen has a carcinogenic effect on the human uterus. Investigators throughout the world continue to publish reports demonstrating the effectiveness of tamoxifen for treating both early and refractory endometrial cancer (*16,17,18*). Not surprisingly, contemporaneous publications also continue to emphasize that the controversial nature of the association between tamoxifen and endometrial cancer "is highlighted by data showing a beneficial effect of tamoxifen on recurrent endometrial cancer." (*4*)

Finally, studies attempting to evaluate the relationship between tamoxifen use, benign endometrial changes, and endometrial cancers diagnosed in treated women are generally unable to provide insight into whether tamoxifen is causing endometrial cancers observed in treated women. The majority have failed to examine for endometrial changes before tamoxifen treatment. Several prospective studies starting with baseline information have been conducted, but they have reported inconsistent observations. While one of the most recent reported a "significantly higher incidence" of hyperplasia with atypia or adenocarcinoma in the group having lesions before initiation of tamoxifen treatment, the authors nonetheless conceded that the mechanisms underlying effects of tamoxifen on the uterus have not been established (*10*). Studies on the incidence of tamoxifen-associated benign endometrial changes are also inconsistent at this juncture, with further studies needed (*13*).

The NTP and other RC Program reviewers should not recommend listing tamoxifen as a known human carcinogen when the existence of a causal relationship between tamoxifen use and endometrial cancers is now so controversial within the scientific community.

5. Data from studies designed to answer some of the questions raised by existing study data will soon be available. The anticipated contribution of this information to the debate on cancer causation cannot properly be ignored in any reasonable cause-effect analysis the ultimate aim of which is the informed protection and improvement of public health. Data like this should assist the RC Program in reaching a

convincingly supported conclusion as to whether the best available human evidence establishes that tamoxifen actually causes human cancer. In particular, we note that, at this date, the results of the NCI-sponsored study headed by Dr. Leslie Bernstein have not been made public, although publication of the study report is awaited by the medical and scientific communities who are dealing with the listing issue that is now before the Report on Carcinogens Program reviewers.

As previously noted in our comments on the NTP listing proposal, Dr. Bernstein's study, will be, along with the very recent Katase et al. study discussed above, one of the first studies designed specifically to examine the effects of obesity and estrogen or hormone use on the occurrence of endometrial cancer in patients using tamoxifen. Even if the results suggest no more than that obesity and estrogen are "risk modifiers", the obesity effect or estrogen effect may well reduce the current, controversial endometrial cancer risk estimates now attributed to tamoxifen to lower and statistically nonsignificant levels. Preliminary reports suggest that this is precisely what the preliminary data indicate (unpublished data of Dr. Leslie Bernstein, presented to the RC Subcommittee in connection with its October 30, 1997, public meeting).

As noted previously, publication of the NSABP Breast Cancer Prevention Trial data and analyses has not yet occurred; and the published report, and possibly the primary data, will have to be carefully examined with the above issue in mind.

ANIMAL AND DNA ADDUCT DATA:

It remains true that neither rat liver cancer data nor evaluation of DNA adducts have elucidated a mechanism applicable to humans that would support the suggestion that tamoxifen is carcinogenic in the human endometrium or other organs. Research has consistently demonstrated that the results of experimental rat carcinogenesis studies cannot be extrapolated to humans.

Newly published data and analytical reviews confirm earlier indications that rat liver carcinogenicity and rat DNA adduct formation data cannot be extrapolated to the clinical use of tamoxifen (*4*). Supporting this observation is the fact that no new epidemiologic observations in humans have revealed a previously undetected increased risk for liver cancers in breast cancer patients treated with tamoxifen (*2*) Reports uniformly establish large interspecies differences in metabolism, DNA adduct formation, and detoxification between humans and rats exposed to tamoxifen.

As we have noted previously, we believe it is clear under the RC listing criteria that a listing in the "known" category must be supported by sufficient human evidence indicating a causal relationship. Mechanistic or non-human data cannot be used to compensate for a lack of sufficient human evidence. Nevertheless, we address such data here because it appears that they may have contributed to the RC review committee recommendations to date, and because we believe they would support a determination not to list tamoxifen even in category two (*19*).

1. <u>DNA adduct data do not resolve the question of whether tamoxifen acts as a carcinogen in the human endometrium</u>. To date, studies have suggested that human and rat liver microsomes both have the capability of activating tamoxifen to electrophilic metabolites that can form DNA adducts. There is now a clear consensus that both *in vitro* and *in vivo* studies have confirmed that the number of DNA adducts formed in human cells are several orders of magnitude lower than those formed in cells of rats (*7,20*).

It is, for instance, well accepted that the levels of ^{32}P-postlabeled DNA adducts observed in livers of tamoxifen-treated women have been remarkably lower than those seen in the rat (*21*). Current publications also emphasize that adducts potentially attributed to human endometrial tissue have been reported only once, at the level of 2.7 DNA adducts per 10^9 nucleotides -- a level that contrasts starkly with the observations of 30,000 adducts per 10^9 nucleotides (3,000 per 108) which have been associated with rat liver exposure and cancer formation in that species (*23,24,4*)

Additionally, the accuracy of that single report of endometrial adducts is in doubt. Dr. Paul Carmichael, at the recent international conference on tamoxifen, reported on his attempts to reproduce Dr. Hemminki's findings using independent tissue samples from tamoxifen-exposed women, and a refined and enhanced HPLC methodology. He concluded that the adducts were probably *endogenous species* or *artifacts*, and that they did *not* implicate a genotoxic mechanism for carcinogenicity (*25*). And other researchers have critiqued the Hemminki work (*22*). Hemminki and colleagues themselves stated in their published article that the adducts they observed could not be attributed to endometrium "with any certainty", since the samples used in the study contained blood and stromal cells (*26*) Since current research appears to confirm that the Hemminki adducts are not attributable to endometrial cell DNA, such data should not be used to support conclusions concerning human carcinogenicity; and, taken together with the data on obvious inter-species numerical adduct disparity and the well-recognized inter-species variability in the effects of hormone-like substances, the research casts serious doubt on the human relevance of the animal cancer data.

It is also a matter of current emphasis that, although tamoxifen-induced adducts in rat uteri have been reported in one study, DNA adduct levels reported in the rat uterus were remarkably lower (6 per 10^9 nucleotides) than those typically observed in rat livers (*27*). These results further attest to the inapplicability of rat liver data to human endometrial cancer. Because the rat uterus is an organ in which rats do not develop tamoxifen-associated cancer, such observations provide further evidence that the presence of low levels of adducts in an organ system do not indicate a specific tumorigenic risk for that tissue.

Moreover, this sole report of adducts in the rat uterus has not been replicated, including in attempts by a recent long-term study. In concluding their 1997 published data, Li and colleagues could say no more than that "[f]urther understanding of the metabolic differences in rat and human endometrium is required to better assess the carcinogenic risk that TAM poses to the human endometrium." (*28*)

A recent review article puts these observations into greater perspective by examining identified DNA adducts in comparison to endogenous DNA adduct levels, known to range from 1 adduct per 10^8 nucleotides to 1 adduct per 10^5 nucleotides. The review quotes a scientific panel which emphasized: "The detection of DNA adducts in a tissue does not necessarily indicate a specific tumorigenic risk for that tissue." (*29*) This same review also emphasizes that the biological significance of all DNA adducts is dependent on (a) their persistence over time, cell replication, and the efficiency with which the adduct is converted to an actual mutation; (b) whether the mutations occur in a critical gene; and (c) the countervailing influences of repair and DNA adduct removal (*29*).

In concluding the session on DNA adducts at the 1997 international conference on tamoxifen, Professor Lewis Smith addressed the uncertainty of these data. His closing comments emphasized that doubts remain as to whether tamoxifen-induced adducts occur in humans at all. He further acknowledged that science was not in a position to resolve the question of the relevance of the experimental animal research to tamoxifen patients (*9*).

2. <u>As more information on interspecies differences is developed, data suggest that tamoxifen DNA adducts are not a likely mechanism affecting human organ systems</u>. Recent publications have given great emphasis to interspecies variations, the "profound differences in rodent and human metabolism of tamoxifen", and an apparent ability of human cells to more adequately remove DNA adducts via detoxifying enzymes (*2*).

Previously, it has been reported that a higher concentration of alpha-hydroxytamoxifen is formed in the rat than in human liver microsomes, which might explain tamoxifen liver carcinogenicity in rats as contrasted with humans (*30*). Additional and dramatic interspecies differences, addressed neither by IARC nor by the RC review committees, can be found in the primate work of Comoglio and colleagues (*31*).

In studying the effects of tamoxifen on male and female rhesus monkeys, the authors found evidence that monkey livers accumulated the N,N-didesmethyl derivative tamoxifen metabolite, which is a powerful inhibitor of drug metabolism. The inhibitory metabolite also accumulated in the microsomal fraction in monkeys (*31*). They also observed that the level of ^{32}P-postlabeled DNA adducts produced in the monkey livers was considerably lower than that in similarly treated rats (*31*).

They also reported that while rats demonstrated a marked increase in covalent binding to microsomal protein, the level of covalent binding in treated monkeys was not greater than in controls. Providing yet another contrast to the rat, another primate, the marmoset, failed to develop phenotypically altered liver foci after tamoxifen treatment (*31*).

Extending their research to human tissue, Comoglio and colleagues observed that addition of the N,N-didesmethyltamoxifen metabolite significantly reduced the extent of covalent binding in both human and rat microsomes *in vitro*. They concluded that accumulation of the inhibitory metabolite in the liver of primates may be acting to inhibit tamoxifen bioactivation and the formation of adducts. They further concluded that this inhibitory metabolite may protect against the development of tamoxifen-induced liver cancer in humans and other primates (*31*).

Finally, these investigators recalled research indicating that the inhibitory metabolite N,N-didesmethyltamoxifen is found also in the serum of women taking tamoxifen (*32*). Together, these important observations may suggest that the formation of this inhibitory metabolite, and perhaps others, could in fact be protecting against tamoxifen-mediated genotoxicity in humans.

CONCLUSION

The human, animal, and *in vitro* data do not provide adequate support for listing tamoxifen in the *Report on Carcinogens*.

The human evidence has not established a causal relationship (*not* a *suspected* causal relationship) between tamoxifen use and the development of endometrial cancer. Although tamoxifen therapy has been associated, in some study groups, with increased diagnosis of endometrial cancer in breast cancer patients, as more data have accumulated over the last several years, many reviewers and investigators have concluded that there are substantial uncertainties which remain to be explored, and whether such data warrants a causal inference is controversial.

Data from animal carcinogenicity studies, and evaluations of tamoxifen genotoxicity and the production of DNA adducts, do not provide mechanistic explanations to support a cogent biological theory for endometrial cancer (or liver cancer) causation in tamoxifen-treated patients. The data, in fact, continue to demonstrate strong interspecies differences and the inapplicability of animal data to human clinical treatment.

POSTSCRIPT

The essential purpose of the Report on Carcinogens Program is to protect, not harm, public health. It is therefore of utmost importance to recognize the low statistical risk estimates, the controversy surrounding them, and the comparative detriment to public health that an inaccurate and premature conclusion could cause. The protection of public health provides no independent justification for listing tamoxifen in the *Report on Carcinogens, Ninth Edition* before there is sufficient scientific evidence to convince the scientific and medical communities that the listing determination can be made with a high degree of confidence. Clearly, the evidence is regarded by many experts as far from convincing at this time.

Breast cancer is a leading killer of women. It accounts for 20% of all cancers throughout the United States. It is currently estimated that 1.5 million women in the United States alone will be diagnosed with breast cancer in this decade. It is expected that 500,000 of these women will die of their disease (*33,34*).

Adjuvant tamoxifen treatment is a proven therapy for breast cancer which is used by over 2 million women worldwide. It is a therapy for breast cancer which has been proven to be effective. It reduces the number of patients whose treatment fails, reduces the otherwise high level of recurrences of breast cancer, and reduces metastases (*33*). Tamoxifen is the only single therapeutic agent that has been proved to produce a survival advantage as well as reduce the incidence of new cancers in the second breast (*35*). Tamoxifen has become the agent of choice in the management of breast cancer. Since its introduction in the 1970s for the treatment of metastatic breast cancer in postmenopausal women, tamoxifen has become the therapeutic treatment of choice for a spectrum of other breast cancer patients, including men with metastatic breast cancer. In extensive clinical trials, tamoxifen remains consistently associated with improved overall survival, improved disease-free survival, and reduced risk of contralateral breast cancer. Moreover, the recent results of the Breast Cancer Prevention Trial have demonstrated the breast cancer prevention benefits of tamoxifen in higher-risk women. The public health benefits of tamoxifen are undisputed.

Zeneca has elsewhere detailed the very real potential that the proposed listing could frighten patients, cause confusion, detrimental patient noncompliance with an otherwise life-saving prescribed treatment regime, and lead to the detrimental effects of stress upon patients fighting against the reality of recurrent breast cancer. The potential adverse public health consequences should alone cause RC Program reviewers and officials to reconsider this proposed listing as unwise.

Reinforcing these concerns is the fact that, even if additional data were to support a determination of carcinogenic risk, current data indicate the risk of endometrial cancer to individuals prescribed tamoxifen is relatively low. It is not excessively aggressive; it is typically symptomatic and readily identified by physicians caring for breast cancer patients; and it is a cancer with a high degree of curability. Thus, the population risk and the individual risk should not instill a sense of urgency to list in the name of protecting public health from a significant threat.

In sum, any RC Program decision to list a substance -- particularly a pharmaceutical -- as a human carcinogen should be cautious, well-considered and informed. Here, the potentially significant adverse effects of such a listing on patient outcomes is an undeniable, additional and important reason why NTP's conclusions about tamoxifen should not be premature. This evaluation must follow a deliberate, open-minded, critical analysis of all reasonably available data -- and should not be released in advance of clear, non-controversial, biologically coherent, human evidence supporting a listing decision. Under the circumstances at hand, the proposed listing can only be discouraged.

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